

UKRAM STUDY

Proposed Changes to the Scientific Protocol of Thyroid Cancer and other Thyroid Disease in Ukraine Following Chernobyl Accident.

On May 10, 1995, the document entitled, "Arrangement for Cooperation Between the United States Department of Energy and the Ministry of Health of Ukraine on the Implementation of the Scientific Protocol for the Study of Thyroid Cancer and Thyroid Disease in Ukraine following the Chernobyl Accident" was signed by representatives of both parties. Since the implementation of the Protocol in June 1996, the Project Program Directors from both Ukraine and the US have determined the need for modifications to the original document. The following are the Ukrainian and US proposed changes:

Cover Page	Section Number	Ukraine	US
	J. METHODS	<u>Current text:</u> (Summary of last part of paragraph 6.) A pilot investigation will be carried out of the content of ^{131}I in the soil and other objects in the environment and possibilities of determining ^{14}C concentration in annual tree rings will be studied. <u>Proposition:</u> Delete the entire text: "Thus, a pilot study...tree rings will be explored." <u>Reason:</u> These studies were not carried out because of the high cost of these analyses.	<u>Proposition:</u> Add the following (text at the end of paragraph 2: "Efforts should be made to collect an electronic database of all the reliable information released to the deposition of the ground and on the environmental concentrations of ^{131}I for the territory of Ukraine."). <u>Proposition:</u> Delete sentence 3 in paragraph 1: "Thus a pilot study...radiation measurements." Replace with: "A pilot study on the utility of contemporary measurements of ^{131}I in soil is in progress in Belarus. If this pilot study provides encouraging results for the prospect of decreasing the uncertainty in calculated thyroid doses, a measurement program of ^{131}I in Ukrainian soils will be undertaken."
	3.1.4. Contribution of External Irradiation and of Internal Irradiation from Radioiodine to the Thyroid Dose	<u>Current text:</u> (Summary) Pilot study will be performed to evaluate the need for determining total radiation dose in certain materials by means of thermoluminescence (ceramics, porcelain, etc.). <u>Proposition:</u> Delete the entire text: "Thus, a pilot study...presented in Section 3.4.1." <u>Reason:</u> Pilot studies showed that there is no need for this method.	<u>Proposition:</u> As ^{131}I seems to be fixed in the upper layers of soil, there is no urgency to carry out this pilot study in Ukraine. The results of the study currently analyzed in Belarus will indicate whether it is helpful to carry out a similar study in Ukraine.

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3.1.7 Summary of Unsolved Dosimetric Problems	<p>Proposition: Add the following two statements to the list of unresolved dosimetric problems:</p> <ul style="list-style-type: none"> • Use of the atmospheric transport model to reconstruct the dynamics of radioiodine contamination in the populated points of the controlled regions. <p>Reason: This is important in refining dose estimates based on direct measurement of the thyroid gland activity and for reconstruction of radiation doses from short lived iodine isotopes.</p> <ul style="list-style-type: none"> • Development of a new model for iodine metabolism in organisms, including the system "Mother-Offspring". <p>Reason: This is necessary for the refining radiation doses on thyroid gland of the offspring and radiation doses received by children from short lived isotopes.</p>	<p>Proposition: Delete the footnote: "Activities identified in this section may eventually be carried out as part of a separate collaborative effort (i.e., a "Dosimetric Support Project")."</p> <p>Reason: DOE decided not to fund this study.</p>
3.3 CLINICAL AND DIAGNOSTIC METHODS FOR THE INTENSIVE AND EXTENSIVE SAMPLES	<p>Current text: (Summary of paragraph 1) During the first stage of this study, medical examinations will be carried out in six regional medical centers, as well as four mobile teams will be used. Stationary centers will be Kyiv (2) in the Research Center of Radiation Medicine and in Institute of Endocrinology and Metabolism, in Chernykhiv and Zhytomyr. Mobile teams will be based in the Institute of Endocrinology and Metabolism (3 teams) and in the Research Center of Radiation Medicine (1 team).</p> <p>Proposition: "The stationary center is located in the Institute of Endocrinology and Metabolism. 4 Mobile teams and the stationary medical team for performing medical examination of project candidates will be based in the Institute of Endocrinology and Metabolism."</p>	<p>Proposition: The fixed medical centers in the Ukraine need to be redefined.</p>

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3.3.1 Palpation and Ultrasound Examination	<p><u>Current text:</u> (Table 3.7) WHO classification (0, 1A, 1B, 2, 3) is noted</p> <p><u>Proposition:</u> Use of simplified WHO classification is recommended: 0, 1, 2.</p>	<p><u>Proposition:</u> Replace Table 3.7 with: "Table 3.7. Eliminate the old classification of goiter size, substitute the new WHO classification:</p> <p>Grade 0 = no goiter (that is, no thyroid enlargement)</p> <p>Grade 1 = thyroid enlarged but not visible with neck in normal position.</p> <p>Grade 3 = thyroid enlarged and visible with neck in normal position.</p>
3.3.2. Ascertainment of Thyroid Cancer	<p><u>Proposition:</u> Add the following points:</p> <ul style="list-style-type: none"> • Perform intraoperative and post-surgical histologic study of the biopsy material of all forms of thyroid gland pathology in patients diagnosed during screening. • Carry out retrospective analysis of clinical-morphologic registry of thyroid cancer based on the identified cohort members already operated on with the following pathomorphologic analysis of identified cases. • Continue the so called "passive screening" among all individuals, residents of Kyiv, Zhytomyr and Chernihiv Oblasts, operated on for thyroid gland disorders in the Institute of Endocrinology and Metabolism with the goal of identifying among them cohort members. Perform pathomorphologic analysis of identified cases. • Establish pathomorphologic bank of UkrAM Project with the goal of possible additional verification or more detailed scientific studies. <p><u>Reason:</u> These points were absent in the original protocol.</p>	

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3.3.3. Ascertainment of Hypothyroidism	<p><u>Current text:</u> Lists determination of thyrotrophic hormone, free and total thyroxine.</p> <p><u>Proposition:</u> Determine only thyrotrophic hormone.</p> <p><u>Reason:</u> Financial restrictions.</p>	<p><u>Proposition:</u> Delete sentence 5: "If free T-4... to the first year." Replace with text: "Hypothyroidism to be ascertained by serum TSH on every visit, with Free T4 or T4 done whenever the TSH is abnormally high or low."</p>
3.3.4. Ascertainment of Iodine Nutrition		<p><u>Proposition:</u> Eliminate the entire text of this paragraph; substitute the following: "Iodine nutrition to be ascertained by measuring urine iodine content of a random urine sample on every subject at the first visit. This will perhaps be repeated at a time to be decided at a later date. In particular, sampling of a subset of subjects based on geographical distribution will not be done, 24 hour urine collections will not be done, urine creatinine will not be measured, and samples will not be sent to the University of Massachusetts for verification."</p>
3.3.5. Ascertainment of Lymphocytic Thyroiditis		<p><u>Current text:</u> Serum obtained under 3.3.1.3. will be used to measure anti-thyroid peroxidase (ATPO) at 1 or 2 year intervals.</p> <p><u>Proposition:</u> In sentence 1, delete the text: "at 1 or 2 year intervals" and substitute: "anti-TPO to be done on every visit, followed by anti-Tg if positive."</p>
3.3.6. Ascertainment of Hyperparathyroidism	<p><u>Current text:</u> Serum obtained under 3.3.1.3 at 1 or 2 year intervals will be used to measure calcium and albumin.</p> <p><u>Proposition:</u> Change "calcium and albumin" to "calcium only."</p> <p><u>Reason:</u> Financial restrictions.</p>	<p><u>Proposition:</u> Delete the entire text and substitute: "Hyperthyroidism to be ascertained by serum ionized calcium on every visit. When elevated, PTH immunoassay will be done in a reference laboratory."</p>
3.3.7. Laboratory Testing		<p><u>Proposition:</u> Delete the second sentence starting with "Selected duplicate...in Worcester."</p>
3.4. INTERVIEW AND QUESTIONNAIRE PROCEDURES AND EXAMINATION RECORDS		<p><u>Proposition:</u> Under "o Tests performed: eliminate T-4, T-3 and Albumin."</p>
3.4.2. Information from Medical Examination		<p>✓</p>

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4. STANDARDIZATION AND QUALITY CONTROL		<u>Proposition:</u> Delete.
4.1. DOSIMETRY		<u>Reason:</u> Such participation in international model variation studies could be decided on an ad hoc basis.
4.1.6. Participation in International Model-Validation Studies		<u>Proposition:</u> Delete the last sentence in the paragraph: "If kits... between kits."
4.4. LABORATORY PROCEDURES		<u>Replace with:</u> "Procedural changes and new equipment will require overlap time during which duplicate tests will be run to assure reproducibility."
4.4.2. Kits for Testing Thyroid Function		<u>Proposition:</u> Delete the text in its entirety. Replace with: "Serum assays will be performed in single determinations."
4.4.3. Individual Runs		<u>Proposition:</u> Delete the second sentence in its entirety.
4.4.5. Inter-laboratory Comparisons		
4.5. PATHOLOGY	<u>Current text:</u> A panel of thyroid gland pathologists (at least three, one of whom is in the U.S.) will review all pathology slides and will recut blocks as required for optimal examination.	<u>Proposition:</u> Two pathologists will determine pathomorphologic diagnosis in the pathology laboratory. Detailed description of the preparations will be recorded on the pathomorphologic form. In complicated cases of differential diagnosis immunohistochemical evaluation will be mandatory, such as evaluation with thyroglobulin and calcitonin antibodies in cases suspicious medullar or anaplastic carcinoma of, when lymphoma of thyroid glands is suspected, with antibodies to leukocyte antigen.
4.5.1. Histopathology		All histologic preparations and the completed forms will be submitted to expert pathologists in the U.S. when necessary. Additional cuts may be made from the archival paraffine blocks for additional morphologic and immunohistochemical studies.
		<u>Reason:</u> Absence of quality control measures where during differential diagnosis of various thyroid gland carcinomas.

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4.5.2. Aspiration Cytology		<p><u>Current text:</u> An expert cytopathologist will review the cytology slides for adequacy and accuracy of diagnosis at least 4 times a year.</p> <p><u>Proposition:</u> Delete the text "at least 4 times a year" Replace with: "The U.S. consultant, based on most recent experience, will determine the frequency of reviews; 4 reviews a year may not be required."</p>
5. DATA COLLECTION, STORAGE, AND RETRIEVAL	<p><u>Current text:</u> (Summary) Results of screening observations will be entered into the computer directly following examination.</p> <p><u>Proposition:</u> Eliminate this text.</p>	<p><u>Reason:</u> The screening results will be entered from hard copies into the computer at the DCC; they cannot be entered directly during the examination for technical reasons.</p>
5.2. DATA ENCODING AND VERIFICATION SYSTEM		<p><u>Proposition:</u> Delete.</p>
5.3. DATA RECORDING STORAGE, AND ANALYSIS RESOURCES		<p><u>Proposition:</u> Delete the text in its entirety. Replace with: "Each ultrasound system will have an image digitizer (Camtronics Magneto Optical Disk (MOD) recorder). A standardized set of images will be recorded for each patient in whom normal findings are noted, and extra images will be recorded when abnormalities are found."</p>
5.3.1. Computer Requirements		<p><u>Proposition:</u> Add the following text under this new section: "Ultrasound images recorded on MOD disks will be backed up on DAT tapes at the DCC. Peripherals on the DCC system will include a DAT tape, MOD read/write device, and a R/W CD-ROM along with the other standard devices specified elsewhere. The DCC will transfer image data from the MOD disks to DAT tapes for long term archiving at a safe, remote place and will rewrite images onto CD-ROM disks in a format suitable for review on standard PCs located at or near the Ultrasound clinical units."</p>
5.3.2. Ultrasound Data		<p><u>Proposition:</u> Delete the text starting with line 6; "Resource requirements" ...and ending with "Center for Radiation Medicine."</p>
5.3.3. (new)		
7. IMPLEMENTATION		<p><u>Proposition:</u> Delete the text starting with line 6; "Resource requirements" ...and ending with "Center for Radiation Medicine."</p>

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7.1. PERSONNEL		<u>Proposition:</u> Delete sections 7.1; 7.1.1; 7.1.3; 7.1.4
7.1.1.2. Staffing Needs for the Mobile Screening Teams	<u>Current Text:</u> (Summary) Mobile team staff will consist of 2 endocrinologists, 2 ultrasonographers, 3 nurses, and 2 drivers.	<u>Proposition:</u> The mobile team staff will consist of 1 endocrinologist (team chief), 1 ultrasonographer, 1 technician for blood and urine collection, 1 US operator, 1 interviewer-dosimetrist, 1 epidemiologist-contact person, 1 driver.
	<u>Reason:</u> Experience gained in the field dictates this composition.	
	<u>Nota bene:</u> additionally composition of other teams should be changed according to the composition of the project members.	
7.2. EQUIPMENT		<u>Proposition:</u> Delete in its entirety.
7.3. SUPPLIES		<u>Proposition:</u> Delete in its entirety.
7.4. PATTERN OF BI-NATIONAL COLLABORATION		<u>Proposition:</u> Add at end of paragraph 2: "(c) Local assistance needed to supplement the salary of the Ukrainian personnel working on the study."
7.5. FUNDING		<u>Proposition:</u> Delete the heading 7.5.1. In the UKRAINIAN BUDGET paragraph: second line substitute "salaries of" for "paying"; delete in lines 3-5 the text: "purchase of such equipment and materials which are not stipulated in the protocol as a U.S. responsibility,"

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7.5.2. Sources of Funds		Proposition: Delete in its entirety.
APPENDICES		Proposition: Delete Appendices A and B; update American Organizational chart to be added to Appendix C. Delete or update Appendix D.

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10. PROJECT MANAGEMENT 10.1. ADVISORY COMMITTEE	<p>Proposition: <u>Bi-national Advisory Group</u></p> <p>Ukrainian and NCI authorities will be assisted by a <u>Bi-National Advisory Group</u> consisting of 10 members, five to be named by Ukrainian Ministry of Health and five by the U.S. National Cancer Institute (after consultation with other U.S. sponsoring agencies). Nominations should reflect the well-established reputation of each candidate from the following areas of expertise: endocrinology, radiation biology, radiation dosimetry, radiation epidemiology and clinical sciences/pathology.</p> <p>Following its establishment the Advisory Group will be self-perpetuating body selecting future members from among those nominated by the sponsoring agencies and its own membership.</p>	<p>Members of the Bi-National Advisory Group will serve five-year terms except that, initially, in order to provide reasonable continuity, the candidates will be appointed for three-, four-, five-, six- and seven-year terms from each national authority. Members may not serve more than two terms. Project staff may not serve as members of the Advisory Group. Former staff members should observe a two-three year hiatus from any involvement in project operations.</p> <p>The Advisory Group will select its own co-chairmen, one Ukrainian and one American (the latter would have already been selected by American membership as the Chairman of the American moiety). The Bi-National Advisory Group will meet at least once a year in Ukraine. It may hold other meetings when necessary or upon request from either the Ukrainian or the U.S. Project Director. The co-chairmen will jointly administer the activities of the Advisory Group including such matters as the agenda, number of meetings per year, alternation of chairmanship, etc.</p> <p>The Advisory Group will respond to requests for advice from the Ukrainian and American Project Directors and will initiate its own agenda topics and investigations. It will be responsible for (1) recommendation of changes in the governing research protocol based on suggestions made to it by either the Ukrainian or the U.S. Project Director, or on its own observation, (2) review of budgets presented by the Ukrainian and U.S. Project Directors (budget approvals are the responsibility of the Ministry of Health in Belarus and the NCI director in the U.S.).</p>

<p>(3) review of the progress of the work on the basis of official reports; e.g., the quarterly reports of the Ukrainian Project Director, information presented at its meetings, reports of site visits, and its own investigations, and (4) advice on publication policy. With the approval of the co-chairmen, data created by project activities will be made available to individual Advisory Group members for informational and review purposes. The Advisory Group will determine its own agenda and operating rules, including the rotation order of individual members; the Group has the right to close the meetings to convene in executive sessions. The Ukrainian Project Director will provide secretarial and other logistical support for the Group's meetings and activities in Ukraine and the U.S. Project Director for meetings in the U.S. The official communication language will be in English. The Project Directors shall be responsible for providing competent translations and interpreters. Travel expenses for the American component to Belarus or Belarussian to U.S. will be covered by the American side.</p>	<p>Proposition: The Project Directors will be responsible or scientific activities (e.g., clinical, laboratory, dosimetric, and epidemiologic), for administration (e.g., personnel, data management, training, fiscal matters, allocation of resources), for preparation of required reports, communication with the press and with various entities of the governments. In their respective areas, they will be responsible for logistic support for the Bi-National Advisory Group. Reallocation of supplies and equipment provided by the U.S. Government will require consent of the U.S. side. One of the crucial tasks for the Ukrainian Project Director is the appointment of a Quality Assurance Officer.</p>
<p>10.2. MANAGEMENT</p>	